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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/531,036	04/12/2005	Karsten Eulenberg	2923-696	7034

6449 7590 10/05/2007

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ART UNIT	**PAPER NUMBER**
1632	

NOTIFICATION DATE	DELIVERY MODE
10/05/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PTO-PAT-Email@rfem.com

Office Action Summary	Application No.	Applicant(s)	
	10/531,036	EULENBERG ET AL.	
	Examiner	Art Unit	
	Anoop Singh	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *36-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *36-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/12/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The Examiner prosecuting this application has been changed. Any inquiries relating to the examination of the application should be directed to Examiner Singh. The telephone number is provided at the end of this office action.

Claims 1-35 are cancelled; claims 36-38 are pending; claims 36-38 are under current examination.

Election/Restrictions

Applicant's election with traverse of claims 36-38 directed to a method of treating metabolic syndrome by administering a nucleic acid molecule encoding AAC97073 (MEKK1) in the reply filed on August 21, 2007 is acknowledged. The traversal is on the grounds that the arguments as to supporting restriction is applicable to a non provisional application which is not governed by the PCT rules regarding unity of invention. In response, it is noted that restriction requirement sent on January 12, 2007 required applicants to elect one nucleic acid encoding a protein from table 1 and also discussed that different groups were not so linked by the same or a corresponding special technical feature as to form a single general inventive concept. Examiner would agree that subsequent restriction sent on May 22, 2007 did use arguments to support restriction applicable to a non provisional application which is not governed by the PCT rules regarding unity of invention, however, it is emphasized that a single general inventive concept under PCT Rule 13.1 requires the same or corresponding special technical features provided in the following reasons: A) The invention has no special technical feature that defined the contribution over the prior art, or B) Unity of invention between different categories of inventions will only be found to exist if specific combinations of

inventions are present. Those combinations include: 1)A product and a special process of manufacture of said product. 2):A product and a process of use of said product. 3) A product, a special process of manufacture of said product, and a process of use of said product. 4): A process and an apparatus specially designed to carry out said process. 5) A product, a special process of manufacture of said product, and an apparatus specially designed to carry out said process. The allowed combinations do not include multiple products, multiple methods of using said products, and methods of making multiple products, see MPEP § 1850. In the instant case, claims 36-38 are directed to a method of treating metabolic syndrome by administering distinct polynucleotide sequence that have distinct chemical structure and encode different protein. Thus, it follows from the preceding analysis that the claimed inventions encompass multiple methods using distinct compositions that do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the reasons set forth above. Since, restriction between method of using distinct nucleic acid sequence encoding different protein would be same in both US non provisional and under lack of unity, the requirement is still deemed proper and is therefore made FINAL.

Claims 36-38 directed to method that uses nucleic acid encoding protein other MEKK1is withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on August 21, 2007.

Information Disclosure Statement

The information disclosure statements (IDS) submitted on 04/12/2005 has not been considered by the examiner as no copy of any of the publication is provided.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 36-38 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In determining whether Applicant's claims are enabled, it must be found that one of skill in the art at the time of invention by applicant would not have had to perform "undue experimentation" to make and/or use the invention claimed. Such a determination is not a simple factual consideration, but is a conclusion reached by weighing at least eight factors as set forth in In re Wands, 858 F.2d at 737, 8 USPQ 1400, 2d at 1404. Such factors are: (1) The breadth of the claims; (2) The nature of the invention; (3) The state of the art; (4) The level of one of ordinary skill in the art; (5) The level of predictability in the art; (6) The amount of direction and guidance provided by Applicant; (7) The existence of working examples; and (8) The quantity of experimentation needed to make and/or use the invention.

The office has analyzed the specification in direct accordance to the factors outlines in *In re Wands*. MPEP 2164.04 states: "[W]hile the analysis and conclusion of a lack of enablement are based on factors discussed in MPEP 2164.01(a) and the evidence as whole, it is not necessary to discuss each factor in written enablement rejection." These factors will be analyzed, in turn, to demonstrate that one of

ordinary skill in the art would have had to perform "undue experimentation" to make and/or use the invention and therefore, applicant's claims are not enabled.

Claims are directed to a method of a method of treating any metabolic syndrome by controlling the function of a gene and or a gene product which is influenced and or modified by Mekk1 in a patient in need of such treatment by administering to said patient a therapeutically effective amount of a nucleic acid encoding Mekk1 homologous protein or a isoform or a functional fragment or any variant thereof. Subsequent claims limit the nucleic acid molecule to include Mekk1. It is noted that claim 38 limits the method to include genus of variant and functional fragments of nucleic acid encoding CG7717.

The aspects considered broad are the breadth of any subject population for treating any metabolic syndrome by controlling any gene and or gene product that is influenced and modified by Mekk1 polypeptide, using any naked DNA or any vector that could be used for administering the nucleic acid composition for treating any metabolic syndrome, any method of administration to affect metabolic syndrome, and transgene not operably linked to expression control elements a critical limitation not described in claims.

The nature of such invention is within the broad genera of gene therapy, and gene therapy is not generally enabling of Applicant's invention due to problems with, *inter alia*, targeting and expression of transgenes at therapeutically effective level by administering composition via any route and method in any tissue. For purposes to be shown in the state of the prior art, the question of lack of enablement is discussed.

The invention broadly relates to a method of treating obesity and/or diabetes mellitus and/or metabolic syndrome by administering nucleic acid encoding gut feeling (guf), GadFly, GadFly, rdgB, Mekk1, Ady43A, GadFly or PP2A-B' homologous proteins (pages 1 and 11). The invention is based in part on the discovery that that guf, CG3811, CG30346 (CG8080), rdgB, Mekk1, Ady43A,

CG14816, tws, or PP2A-B' and the polynucleotide encoding these, are involved in the regulation of triglyceride and/or glycogen storage and therefore energy homeostasis (page 11 bridging to page 12). Page-21-43 describes diagnostic and therapeutic use of the disclosed composition. Example 1 of the specification teaches measurement of triglyceride and/or glycogen in Drosophila (see page 51 of the specification), while examples 2 and 3 identifies Drosophila genes that are associated with energy homeostasis and its human homologous genes and proteins including Mekk1 (see page 53, 56 and table 1). In addition specification also teaches expression profile to confirm the relevance of the proteins of the invention as regulators of energy metabolism in mammals. It is noted that mitogen activated protein kinase kinase 4 (Map3k4) is expressed in several mammalian tissues, showing highest level of expression in muscle, hypothalamus, brain, and heart and higher levels in further tissues. Furthermore Map3k4 is expressed on lower but still robust levels in pancreas and bone marrow of wild type mice (see figure16A). In addition specification exemplifies that the expression of Map3k4 is down-regulated in pancreas, hypothalamus, kidney, and bone marrow of fasted mice compared to wild type mice, while the expression of Map3k4 is down-regulated in the brain and bone marrow and up-regulated in the hypothalamus of ob/ob mice compared to wild type mice (see figure 16 B, see page 73, cline 15-30).

However, such broad disclosure does not demonstrate the information required by the Artisan to reasonably predict that any transgene can be expressed in cells of any subject or human at minimum effective levels for therapeutic response in the treatment of any metabolic syndrome by controlling the function of gene and or a gene product which is influenced by Mekk1. The specification does not provide any specific guidance for expressing the nucleic acid at therapeutic effective level in any cells of any patient.

As a first issue, the claims as recited do not require the nucleic acid encoding a Mekk1 or its variant protein is part of an expression vector operably linked to any

regulatory sequences, such as any promoter that permits the expression of said nucleic acid molecule in cells or tissue. Given the broadest reasonable interpretation these claims embrace any promoter that would allow the expression of nucleic acid encoding Mekk1 protein or its variant nonspecifically in any cell including adipose cells. The specification only provides guidance with respect to use of expression vectors encoding nucleic acid molecules (Specification page 18, lines 5-25). It does not provide guidance on the use of naked nucleic acid molecules, lacking a promoter in the claimed method. Further, the literature at the time of filing does not provide guidance on how to get RNA polymerase to efficiently prime to a DNA strand that lacks a promoter. It is noted that De Palma (Hum Gene Ther. 2003; 14(12): 1193-206) describes the efficiency and specificity of vector expression *in vitro* in a panel of human primary cultures. The vectors containing promoter and enhancer sequences from the gene showed specificity of expression in endothelial cells in vitro and in vivo. It is emphasized that De Palma et al show that intravenous delivery into tumor-bearing mice the Tie2 vector targeted expression to the ECs of tumor vessels while LVs carrying the PGK or CMV promoter gave widespread GFP marking in ECs and non-ECs of tumors and other organs. Therefore, it is apparent that a delivery of polynucleotide encoding a Mekk1 comprising any promoter or regulatory sequence would not provide tissue specific expression of transgene that would be required for the effective therapeutic gene therapy as embraced by claims. Therefore, the skilled practitioner would be unable to practice the invention as claimed.

As s second issue, claims embrace administering a patient a therapeutically effective amount of a nucleic acid molecule encoding Mekk1, homologous protein or isoform or a functional fragment or variant. The specification does not provide any guidance on how to identify variants and isoforms of Mekk1 encompassed by the scope of the claim that are capable of being used in the claimed invention. The specification and claims embrace nucleotide sequence of Mekk1 homologous nucleic

acids, a nucleotide sequence which hybridizes to the nucleic acid of the invention, a sequence which encodes a polypeptide which is at least 85%, identical to the amino acid sequences of Mekk1 homologous protein and any sequence which differs from the nucleic acid of the invention by mutation which causes an alteration, deletion, duplication and/or premature stop in the encoded polypeptide or a fragment (Specification, page 11). Further, it may also include isoform. However, the specification does not provide any guidance on the identity shared by Mekk1 with any other Mekk1 isoform. Similarly, the specification does not provide any guidance on what sequence regions or functional domains must be conserved amongst any of the claimed polynucleotide in order for the resulting polypeptide to function (emphasis added) in the therapeutic method. This specification is silent about specific residues and functional domains that must be conserved in any variant of the Mekk1 homolog protein encoded by a polynucleotide that can hybridize to or has 95% or higher identity with Mekk1. The lack of guidance in the specification would force the skilled practitioner to guess as to how to practice the invention. Such guessing would require extensive and undue experimentation. Applicant should note that "case law requires that the disclosure of an application shall inform those skilled in the art how to use applicant's alleged discovery, not to find out how to use it for themselves." *In re Gardner* 166 USPQ 138 (CCPA) 1970.

As a third issue, instant claims are intended for the treatment of any metabolic syndrome by administering a patient an effective amount of nucleic acid molecule encoding Mekk1 homolog protein or its variant, however, gene therapy at the time of the filing of this application was unpredictable since numerous factors complicated the gene delivery art that is difficult to be overcome by routine experimentation. These include, the fate of DNA vector itself, volume of distribution, rate of clearance in tissue, the in vivo consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the

rate of degradation of the DNA, the level of RNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced. These factors differ significantly based on the vector used and the protein being produced (Ecke et al Goodman & Gilman's The Pharmacological basis of Therapeutics, McGraw-Hill, New York, NY. pp 77-101). While progress has been made in recent years for *in vivo* gene transfer, vector targeting *in vivo* to be desired organs continued to be unpredictable and inefficient. The specification contemplates variety of expression vector to express sequences encoding the proteins or fusion proteins including viral expression vector such as baculovirus, adenovirus, adeno-associated virus, lentiverus and retrovirus (see page 19, lines 10-11). The specification provides no guidance in terms of whether transgene delivered by methods known in the art would result in expression of Mekk1 homolog protein for adequate time at a level sufficient to elicit pharmacological response. This is particularly important since prior to instant invention, the state of the prior art effectively summarized by the references of Verma and Somia (1997) Nature 389:239-242 and Pfeifer and Verma (2001) Annual Review of Genomics and Human Genetics.2: 177-211 describes progress made in developing new vectors and also suggest vector targeting *in vivo* to be unpredictable and inefficient. Verma et al., reviews various vectors known in the art for use in gene therapy and problems associated with each implying that at the time of claimed invention resolution to vector targeting had not been achieved in the art (Verma et al., 1997; Pfeifer et al., 2001; entire article; IDS). They highlight some advantages of using retroviral and adeno-associated viral vector in gene therapy but also acknowledge a greater level of skepticism in using these vectors in human (Pfeifer et al., 2001; abstract)(Pfeifer and Verma 2001, Annual Review of Genomics and Human Genetics.2: 177-211, pp 201, Verma et al Annu Rev Biochem. 2005;74:711-38, abstract). The specification merely provides a general description that of potential role and identification of drosophila genes associated with energy

homeostasis, which is not sufficient to provide enabling support because claimed therapy method cannot be actually reduced to practice until the skilled artisan is provided by sufficient guidance to how and how long the transgene expression would be required to attain therapeutic response in a patients. These methods would have required undue experimentation because neither the specification nor the art of record teaches specific guidance for treating complex metabolic syndrome as embraced by the breadth of the claims.

As a fourth issue, instant claims embrace treating a metabolic syndrome by administering via any route a composition comprising a nucleic acid sequence encoding a Mekk1 homologue protein. The specification describes administration of the composition of the invention may be oral, intravenous, intramuscular, intra-arterial, intramedullary, intrathecal, intraventricular, transdermal, subcutaneous, intraperitoneal, intranasal, enteral, topical, sublingual or rectal means (see page 27, lines 25-30 of the specification). It has been difficult to predict the efficacy and outcome of transduced therapeutic genes because several factors govern the expression and/or therapeutic potential of transduced gene *in vivo*. The transduction of target cells represent the first critical step in any gene based therapy, which not only depends upon the type of target cells but also on the choice and/or characteristics of delivery virus or viral vectors. In addition, besides the limitations in gene transfer the problem to selectively target cells *in vivo* is still one of the most difficult obstacles to overcome. For example, upon systemic administration the viral particle may bind to many cells they encounter *in vivo* and therefore would be diluted before reaching their targets. For instance, Gautam et al (Am J Respir Med, 2002;1(1):35-46; abstract) discloses the use of different vector delivery routes to the lung, such as intravenous injection, intratracheal installation, and aerosol with varying degrees of success. They further disclose various barriers to delivery of vectors such as serum proteins during intravenous injection, surfactant and mucus interference during topical applications of vectors. McCluskie

et al teaches that the route of delivery of DNA vaccine influences immune responses in laboratory animals (McCluskie et al (1999) Mol. Med. 5:287-300; Abstract). Specifically, in one study McCluskie et al observed lack of response to non-injected routes of administration of DNA based vaccines, such as oral routes, sub lingual, inhalation and vaginal wall due to variation in transfection efficiency (Abstract). The specification fails to provide an enabling disclosure for the claimed invention because the specification fails to provide sufficient guidance as to how an artisan of skill would have practiced the claimed method in any subject including humans by administering compositions comprising nucleic acid via any route. An artisan would have to carry out extensive experimentation to make and use the invention, and such experimentation would have been undue because art of the gene delivery was not routine rather it was unpredictable and specification fails to provide any guidance as to how the claimed method would have been practiced.

As a final issue, instant claims embrace treating a variety of complex metabolic syndromes by controlling the function of gene and/ or gene product which is influenced by the Mekk1 homologue protein by administering a patient in need a therapeutically effective amount of nucleic acid encoding Mekk1 homologue protein. The specification contemplates treatment of metabolic diseases or dysfunctions, including obesity, diabetes mellitus and/or metabolic syndrome, as well as related disorders such as eating disorder, cachexia, hypertension, coronary heart disease, hypercholesterolemia, dyslipidemia, osteoarthritis, gallstones, or liver fibrosis (see page 5, lines 9-14 of the specification). It is noted that approximately 102 mutations of 64 different genes cause hyperglycemia in mice (see MGI pages titled "Mammalian Phenotype Ontology Annotations" for hyperglycemia http: //www. informatics.jax.org/ javawi2/ servlet/ WIFetch? page=mpAnnotSummary&id=MP:0002138). Hyperinsulinemia is generic to 94 mutations of about 57 genes and increased weight gain is generic to 14 mutations of 11 genes. The specification does not provide any nexus between the

administering Mekk1 to controlling the function of any gene and or gene product, which is influenced and/or modified by Mekk1 for the treatment of genus of metabolic disorder obesity, embraced by the breadth of claims. Liu et al while revising the genetic mechanism of obesity states that "most common form of obesity is considered to be a polygenic disorder arising from the interaction of multiple genetic and environmental factors (Liu et al Curr Mol Med. 2003; 3(4): 325-40see abstract). In the instant case, specification fails to support provide therapeutic effect of claimed composition in any reliable animal model of metabolic syndrome. Given the lack of teachings in the specification and the general unpredictability in the art the skilled practitioner would be unable to predict how to adminster a nucleic acid encoding Mekk1 homologue for the treatment of a complex disorder involving interaction of multiple gene in any tissue to treat any patient including humans without undue and extensive experimentation.

The cited arts clearly indicate an unpredictable status of the gene therapy art pertaining to treatment of metabolic syndrome. Although, specific vectors, promoters, genes, and route of administration might be or may have been effective for treatment of specific disease providing specific therapeutic effect. Gene therapy as a broad-based art is clearly unpredictable in terms of achieving levels and duration of expression of a gene of interest, which results in a therapeutic effect.

In conclusion, in view of breadth of the claims and absence of a strong showing by Applicant, in the way of specific guidance and direction, and/or working examples demonstrating the same, such invention as claimed by Applicant is not enabled. The specification and prior art do not teach a method of *in vivo* delivery of a nucleic acid encoding Mekk1 homologue protein such that it is expressed at therapeutic effective level for desired time in any patient. An artisan of skill would have required undue experimentation to develop/design a suitable vector and practice the method as claimed because the art of gene therapy, vector design and

in vivo delivery and treatment of metabolic syndrome was unpredictable at the time of filing of this application as supported by the observations in the art record.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 36-38 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims are directed to a method of administering a patient a therapeutically effective amount of a nucleic acid molecule encoding Mekk1, homologous protein or isoform or a functional fragment or variant. Subsequent claims limit the nucleic acid encoding Mekk1 homologue to include nucleic acid selected from a group consisting of nucleotide sequence of Mekk1 homologous nucleic acids, isoforms of Mekk1 set forth in table 1 of the specification, a nucleotide sequence which hybridizes to the nucleic acid of the invention, a sequence which encodes a polypeptide which is at least 85%, identical to the amino acid sequences of Mekk1 homologous protein, functional fragments and or variants and any sequence which differs from the nucleic acid of the invention by mutation which causes an alteration, deletion, duplication and/or premature stop in the encoded polypeptide or a fragment (claim 38 and Specification, page 11). The specification has disclosed a sequence of Mekk1 homologue as set forth in table 1.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. . *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111 (Fed. Cir. 1991), clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." *Vas-cath Inc. v. Mahurkar*, 19USPQ2d at 1 117. The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." *Vas-cath Inc. v. Mahurkar*, 19USPQ2d at 1116.

The specification describes Mekk1 homologue sequence without giving any particular structure to function/activity relationship in this single disclosed species for use in the invention as recited. Additionally, to the extent that the claims are intended to encompass variants and fragments, the specification fails to provide any guidance to how modification to Mekk1 homologue can be made while maintaining the required biological activity. It is emphasized that hybridization is also set forth in claims, however the specification does not provide any functional properties to the resulting sequence. For example, a sequence of 50 to100 base pairs from the Mekk1 homologue will hybridize, however if it does not contain the essential motifs that are required for contemplated biological activity, such a sequence will hybridize to the Mekk1 sequence but will not be functional and show contemplated biological activity. The specification does not provide any disclosure as to what would have been the required structure for a other fragments and variants of gene encoding Mekk1 homologue fragments or variants. . There is no evidence on the record of a relationship between the structures of the DNA molecules of any of the

embraced Mekk1 sequence that would provide any reliable information about the structure of DNA molecules within the genus. There is no evidence on the record that embraced Mekk1 homologue sequences had known structural relationships to other smaller fragments. The claimed invention as a whole is not adequately described if the claims require essential or critical elements or motifs which are not adequately described in the specification and which is not conventional in the art as of applicant's effective filing date. In addition, claims are also directed to nucleic acid molecule which are at least 85% identical to a human protein descried in table 1. It is noted that claims also embrace any sequence which differs from the nucleic acid of the invention by mutation which causes an alteration, deletion, duplication and/or premature stop in the encoded polypeptide or a fragment (Specification, page 11). However, specification fails to provide any specific guidance which portion of the sequence could be added or deleted to obtain contemplated biological activity. It is emphasized that a deletion from critical region of sequence may not show contemplated biological activity as protein is highly dependent on the overall structure of the protein itself and the primary amino acid sequence determines the conformation of the protein. It is emphasized that mere identification of one of the fragment would not be sufficient, as the ordinary artisan would immediately recognize that the polypeptide must assume the proper three-dimensional configuration to be active, which is dependent upon the surrounding residues. (see Rudinger in Peptide Hormones, Parsons (ed.), University Park Press: Baltimore, MD, pp. 1-7, 1976). It is emphasized that a deletion from critical region may not show contemplated biological activity as protein is highly dependent on the overall structure of the protein itself and the primary amino acid sequence determines the conformation of the protein. This is also evidenced by studies of Ngo et al that disclose addition or deletions, which are critical to maintain the protein structure/function, will require guidance (Ngo et al., 1994, The protein Folding Problem and Tertiary Structure Prediction, pp492-495). Thus, it is apparent that a

minor structural difference in sequence could result in substantially different activities unless claims necessarily require critical elements in 85% sequence. The specification however has not disclosed the critical region or motifs are required for contemplated biological activity.

Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. *Pfaff v. Wells Electronics. Inc.*, 48 USPQ2d 1641, 1646 (1998).

In the instant case, the claimed embodiments of genus of sequence, other than those set forth in table 1 for Mekk1 sequences encompassed within the genus of fragments and variants that would hybridize or have at least 85% homology or differ the nucleic acid by mutation with instantly claimed sequences lack a written description. The specification fails to describe what DNA molecules fall into this genus. The skilled artisan cannot envision the detailed chemical structure of the encompassed fragments or variant that hybridizes, isoforms with the sequence and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991).

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 UsPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGF'S were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

In view of the above considerations, one of skill in the art would not recognize that applicant was in possession of the necessary common features or

attributes possessed by member of the genus of fragments, isoforms and variants, other than the Mekk1 sequences set forth in table 1. Therefore, Applicant was not in possession of the genus of sequences as encompassed by the claims. *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1404, 1405 held that to fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention."

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 36-38 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. Instant claims recites one method step of administering the nucleic acid composition of the invention, but the does not set forth any positive active steps involved in method/process linking the preamble of treating metabolic syndrome. It is unclear what method /process applicant is intending to encompass. The omitted steps are: whether metabolic syndrome condition is ameliorated. The claim merely recites administering the composition without any active, positive step delineating how up, down or same expression result would actually mean to the treatment method. Claims 37-38 depend on claim 36. Appropriate correction is required.

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anoop Singh whose telephone number is (571) 272-3306. The examiner can normally be reached on 9:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272- 4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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